influence the patch due to the high concentration of tulobuterol. For example, even if the preparation has good quality just after preparing it, with the passage of time there is a possibility that the drug-release pattern becomes different from the pattern at an earlier time because tulobuterol crystallizes in the adhesive layer or its concentration changes.

The object of the present invention is to provide a patch in which tulobuterol is contained in a lower concentration, but the patch has controllability of stable drug-release.

This object is achieved by the present invention, which provides a patch prepared by laminating an adhesive layer consisting of a rubber, an adhesive resin, a plasticizer, 1 to 4 w/w% of tulobuterol as an active ingredient and 0.1 to 3 w/w% of a higher fatty acid (such as a C_{11-22} fatty acid) as a drug release controlling agent on a backing.

In comparing the preparation of the present invention with the preparation disclosed in Nakano et al., they are the same in rubber, adhesive resin, and plasticizer used therein. However the content of tulobuterol contained in an adhesive layer is different from each other, namely the preparation of the present invention relates to one containing a lower concentration of tulobuterol (1 to 4 w/w %), and the preparation disclosed in Nakano et al. relates to one containing a higher concentration of tulobuterol (**not less than 5 wt %**). Furthermore the preparation of the present invention contains a higher fatty acid (such as a C_{11-22} fatty acid) as a drug-release controlling agent as an essential component, but the preparation disclosed in Nakano et al. does not contain such a fatty acid, but rather, contains a **fatty acid ester** such as isopropyl myristate as a solubilizer (an additive).

With regard to item 1 on page 4 of the Office Action, the Examiner argues that Nakano et al. state explicitly that patch formulations using a concentration of tulobuterol within the range claimed instantly (i.e. 3 wt%) are known in the art, and that a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties.

Applicants do not deny that the patch formulations using a concentration of tulobuterol within the instantly claimed range (i.e. 3 wt%) are known in the art. However, such a known patch has many disadvantages, as shown in Comparative examples 2, 3, etc. in the specification, and attempts have been made to improve such a patch. The present invention has no relation at

all with the known patch formulations using a concentration of tulobuterol of 3 wt%, other than this concentration.

In item 2, in addressing Applicants' argument that the patch of Nakano et al. is far inferior to the patch of the present invention in drug permeability, the Examiner argues that the data presented at Table 1 and Fig. 3 do not accurately reflect the scope of what Applicants are claiming. The Examiner further states that Applicants provide no comparison data between a patch formulation with 4 w/w% tulobuterol, and one with 4 w/w% tulobuterol. [It is Applicants' understanding that the Examiner meant to refer to comparison data between a patch formulation with 4 w/w% tulobuterol (present invention), and one with **5** w/w% tulobuterol (Nakano et al.)]

However, as shown in Table 1 and Fig. 3, a patch (2 w/w%) of Example 1 of the present invention is hardly affected in drug permeation over the passage of time, or due to changes of the preservation temperature.

On the other hand, a patch (5 w/w%) of Example 8 of Nakano et al. (Comparative example 6 in the present specification) is greatly affected in drug permeation due to changes of the preservation temperature.

As shown in Fig. 4 of the present application, the permeation of tulobuterol with a patch (3 w/w%) of Example 4 of the present invention is not affected by the passage of time or changes of preservation temperature.

Furthermore, as shown in the Declaration of one of the present inventors enclosed herewith, a patch (4w/w%) of a new example directed to the present invention is hardly affected in drug permeation over the passage of time or due to changes of preservation temperature, compared with a patch (5 w/w%) of Example 8 of Nakano et al. (Comparative example 6).

As explained above, unexpected effect on patches (2 to 4 w/w%) of the present invention have been shown based on a comparison with the prior art, in both the present specification and the attached Declaration, as a result of which any presumption of obviousness which may have been established by the Examiner has been overcome.

In item 3 on page 5 of the Office Action, the Examiner takes the position that the term "fatty acid", as used in the art, includes fatty acid esters; and that Applicants have not given a special definition to the term which would remove fatty acid esters from said definition. The Examiner further argues that fatty acids consist of a lipid portion and an acid portion; that

tulobuterol binds non-covalently to the lipid portion of the fatty acid, which in turn functions as a drug controlling agent; that the lipid portion of the fatty acid ester disclosed by Nakano et al. is identical to that claimed; and that the fatty acid ester disclosed by Nakano et al. will have the same physical property as the fatty acid instantly claimed, i.e., it will act as a drug controlling agent.

However, with all due respect to the Examiner, Applicant take the position that it is common sense for the chemist in the art that "fatty acids" cannot include fatty acid esters, and "fatty acid esters" cannot include fatty acids. Fatty acids and fatty acid esters do not have the same physical and chemical properties.

Applicants do not know that tulobuterol binds non-covalently to the lipid portion of the fatty acid, which in turn functions as a drug controlling agent, but even if this were true, it still does not suggest the presently claimed invention, as discussed above. One of ordinary skill in the art would not have expected that by using a higher fatty acid such as a C_{11-22} fatty acid, a patch containing tulobuterol in the lower concentration of 1 to 4 wt % (compared to a minimum of 5 wt % in Nakano et al.) and having a controlled stable release without being affected due to changes of the preservation temperature could be prepared. From the disclosure of Nakano et al. one would not be motivated to use such a higher fatty acid with the expectation of obtaining the improved patch preparation containing tulobuterol in the lower concentration of 1 to 4 wt %.

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the Nakano et al. reference.

Therefore, in view of the foregoing remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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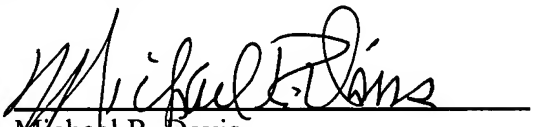
By: 

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